A6
Harrison

Beecham
laboratories

EXECUTIVE OFFICES 501 FIFTH STREET, BRISTOL, TENNESSEE 37620 615-764-5141

January 28, 1980

1/31/80

John S. Harrison

Food and Drug Administration
Bureau of Drugs (HFD-535)
5600 Fishers Lane
Rockville, Maryland 20857

RE: Supplement to Antibiotic Form 6 #62-238
Dicloxacillin Sodium (440.119a)

Gentlemen:

Under approved Form 6 #60-254, Beecham Laboratories' Piscataway, N.J. Plant manufactured, packaged and labelled 250 mg Dicloxacillin Sodium Capsules to be distributed by Ayerst Laboratories, Inc., New York, N.Y., under the trade name Veracillin.

Form 6 #62-238, approved December 31, 1979, authorizes Beecham Laboratories to manufacture, package, and label 250 mg and 500 mg Dicloxacillin Sodium Capsules, at its antibiotics plant in Bristol, Tennessee.

This supplement is being submitted to request approval to manufacture, package and label 250 mg Dicloxacillin Sodium Capsules, packages of 100 capsules, at Beecham's Bristol, Tennessee, antibiotics plant for distribution by Ayerst Laboratories, under the trade name Veracillin (see attached label and package insert).

This supplement is being submitted in triplicate.

Thank you.

Sincerely,

Dennis R. Christian

Dennis R. Christian, Ph.D.
Director, Regulatory Affairs

DRC/hs

Enclosures

cc: FDA (3 copies)

RECEIVED
JAN 29 10 11 AM '80
FDA/BD/HFD-535

011764

VERACILLIN*
(DICLOXACILLIN SODIUM)
CAPSULES

100 Capsules

NOTE: Dispense in child resistant packaging. This package not for household use.

Each capsule equivalent to
250 mg
dicloxacillin

Ayerst CAUTION: Federal law prohibits dispensing without prescription.

Each capsule contains dicloxacillin sodium monohydrate, equivalent to 250 mg dicloxacillin.

Usual dosage: Adults—1 or 2 capsules every 6 hours.
Children—depending on weight.
IMPORTANT: Read complete descriptive literature enclosed.

STORE AT ROOM TEMPERATURE (APPROXIMATELY 25° C)

*Mfr. lic'd. under #734,467.
N79

9405880

Printed in U.S.A.

DISPENSE IN TIGHT CONTAINERS AS DEFINED IN THE U.S.P.

Manufactured by Beecham Laboratories, Div. of Beecham Inc., Bristol, Tenn. 37620
Distributed by
AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

Control No.

Exp. Date

VERACILLIN*

(dicloxacillin sodium) CAPSULES

CAUTION: Federal law prohibits dispensing without prescription.

Description

VERACILLIN (dicloxacillin sodium) is an isoxazolyl penicillin which resists destruction by the enzyme penicillinase (beta lactamase). It is the monohydrate sodium salt of 6-[3-(2, 6-dichlorophenyl)-5-methyl-4-isoxazolecarboxamido]-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid.

Actions

Pharmacology

VERACILLIN is resistant to destruction by acid and is exceptionally well absorbed from the gastrointestinal tract. Oral administration of VERACILLIN gives blood levels considerably higher than those obtained with equivalent doses of any other presently available oral penicillin.

Microbiology

In vitro, VERACILLIN is active against certain gram-positive cocci including most strains of beta-hemolytic streptococci, pneumococci, penicillin G-sensitive staphylococci and, because of its resistance to penicillinase, penicillin G-resistant staphylococci, Dicloxacillin has less intrinsic antibacterial activity and a narrower spectrum than penicillin G.

Disc Susceptibility Tests

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure† has been recommended for use with discs for testing susceptibility to penicillinase-resistant penicillin class antibiotics. Interpretations correlate diameters on the disc test with MIC values for penicillinase-resistant penicillins. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (*e.g.*, urine), in which high antibiotic levels are attained.

Indications

Although the principal indication for VERACILLIN is in the treatment of infections due to penicillinase-producing staphylococci, it may be used to initiate therapy in any patient in whom a staphylococcal infection is suspected. (See Important Note below.)

Bacteriological studies to determine the causative organisms and their sensitivity to dicloxacillin should be performed.

In serious, life-threatening infections, oral preparations of the penicillinase-resistant penicillins should not be relied on for initial therapy.

Important Note

When it is judged necessary that treatment be initiated before definitive culture and sensitivity results are known, the choice of dicloxacillin should take into consideration the fact that it has been shown to be effective only in the treatment of infections caused by pneumococci, Group A beta-hemolytic streptococci, and penicillin G-resistant and penicillin G-sensitive staphylococci. If the bacteriology report later indicates the infection is due to an organism other than a penicillin G-resistant staphylococcus sensitive to dicloxacillin, the physician is advised to continue therapy with a drug other than dicloxacillin or any other penicillinase-resistant penicillin.

Recent studies have shown that the percentage of staphylococcal isolates resistant to penicillin G outside the hospital is increasing, approximating the high percentage of resistant staphylococcal isolates found in the hospital. For this reason, it is recommended that a penicillinase-resistant penicillin be used as initial therapy for any suspected staphylococcal infection until culture and sensitivity results are known.

Dicloxacillin acts through a mechanism similar to that of methicillin against penicillin G-resistant staphylococci. Strains of staphylococci resistant to methicillin have existed in nature and it is known that the number of these strains reported has been increasing. Such strains of staphylococci have been capable of producing serious disease, in some instances resulting in fatality. Because of this, there is concern that widespread use of penicillinase-resistant penicillins may result in the appearance of an increasing number of staphylococcal strains which are resistant to these penicillins.

Methicillin-resistant strains are almost always resistant to all other penicillinase-resistant penicillins (cross resistance with cephalosporin derivatives also occurs frequently). Resistance to any penicillinase-resistant penicillin should be interpreted as evidence of clinical resistance to all in spite of the fact that minor variations in *in vitro* sensitivity may be encountered when more than one penicillinase-resistant penicillin is tested against the same strain of staphylococcus.

†Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M.: Antibiotic susceptibility testing by a standardized single disk method, Am. J. Clin. Pathol. *45*:493, 1966; Standardized Disc Susceptibility Test, FEDERAL REGISTER *37*:20527 - 29, 1972.

*Mfr. lic'd. under ® 734,467

(continued on other side)

VERACILLIN (dicloxacillin sodium) Capsules cont'd.

Contraindications

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

Warnings

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity reactions who experienced severe hypersensitivity reactions when treated with cephalosporins. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other allergens. If an allergic reaction occurs, appropriate therapy should be instituted and discontinuance of dicloxacillin therapy considered. **Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.**

Precautions

As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during prolonged therapy.

The possibility of bacterial and fungal superinfection should be kept in mind during long term therapy. If overgrowth of resistant organisms occurs, appropriate measures should be taken.

This oral preparation should not be relied upon in patients with severe illness or with nausea, vomiting, gastric dilatation, cardiospasm or intestinal hypermotility.

Since experience in neonates is limited, a dose for the newborn is not recommended at this time.

Usage in pregnancy

Safety for use in pregnancy has not been established.

Adverse Reactions

Gastrointestinal disturbances such as nausea, vomiting, epigastric discomfort, flatulence, and loose stools have been noted in some patients receiving dicloxacillin. As with other penicillins, pruritus, urticaria, skin rashes, eosinophilia, anaphylactic reactions, and other allergic symptoms have been occasionally encountered.

Minor changes in the results of liver function tests such as transient elevation of SGOT and changes in cephalin flocculation tests have been reported. The clinical significance of these changes is unknown.

Dosage and Administration

For mild-to-moderate upper respiratory and localized skin and soft tissue infections due to sensitive organisms:

Adults and children weighing 40 kg (88 lb) or more: 125 mg q 6 h.

Children weighing less than 40 kg (88 lb): 12.5 mg/kg/day in equally divided doses q 6 h.

For more severe infections such as those of the lower respiratory tract or disseminated infections:

Adults and children weighing 40 kg (88 lb) or more: 250 mg q 6 h or higher.

Children weighing less than 40 kg (88 lb): 25 mg/kg/day or higher in equally divided doses q 6 h.

Since experience in neonates is limited, a dose for the newborn is not recommended at this time.

Dicloxacillin sodium is best absorbed when taken on an empty stomach, preferably one to two hours before meals.

N.B.: INFECTIONS CAUSED BY GROUP A BETA-HEMOLYTIC STREPTOCOCCI SHOULD BE TREATED FOR AT LEAST 10 DAYS TO HELP PREVENT THE OCCURRENCE OF ACUTE RHEUMATIC FEVER OR ACUTE GLOMERULONEPHRITIS.

How Supplied

VERACILLIN (dicloxacillin sodium) Capsules.

—Each capsule contains dicloxacillin sodium monohydrate equivalent to 250 mg dicloxacillin. In bottles of 100 (NDC 0046-0661-81).

—Each capsule contains dicloxacillin sodium monohydrate equivalent to 500 mg dicloxacillin. In bottles of 50 (NDC 0046-0662-50).

Manufactured by Beecham Laboratories
Div. of Beecham Inc., Bristol, Tenn. 37620

Distributed by
AYERST LABORATORIES INC.
NEW YORK, N.Y. 10017

Revised June 1978. Printed in U.S.A.

9416851

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

DEC 31 1979

Our reference:
62-238 (440.119a)

cc:322/SFishman
NSV-DO
HFD-535 HFD-610
HFD-535/OD HFD-500/DHare
HFD-430/lab.
HFD-332/FGeissel
HFD-332/KWhitley
HFD-530/Dr.Seife
HFD-535/JDHarrison 12/31/79
Prepared by:WEMagner
typ.12/28/79 hb

Beecham Laboratories
Attention: Dennis R. Christian, Ph.D.
501 Fifth Street
Bristol, Tennessee 37620

Gentlemen:

We have completed our review of your Form 6 application dated September 27, 1979, amended October 18, 1979, which provides for the batch certification of dicloxacillin sodium monohydrate capsules, manufactured at your facilities in Bristol, Tennessee. The application is satisfactory. An approved copy is enclosed for your files.

Your firm is now authorized to request certification of batches of dicloxacillin sodium 250 mg. and 500 mg. capsules, manufactured, controlled, packaged and labeled as described in the application.

The application as approved provides for maximum batch sizes of 250 mg. capsules and 500 mg. capsules. An expiration date of 60 months should be used on each batch of the drug submitted for certification, packaged in glass with white metal cap.

Samples from the first three certified batches should be set aside for stability studies. The data from such studies should be submitted at six month intervals the first year and annually thereafter.

The Form 6 application should be kept up-to-date. Any changes in the manufacturing procedures, controls, packaging, labeling or personnel should be submitted as an amendment to the application.

Sincerely yours,

Marvin Seife 12/31/79

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Bureau of Drugs

Enclosure

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

~~NDA NUMBER~~ Form 6
62-238

DATE APPROVAL LETTER ISSUED

TO: Press Relations Staff (HFI-40)

FROM:
- [X] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA
- [X] ABBREVIATED ORIGINAL ~~NDA~~ 6
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [X] HUMAN
- [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

"Dycill" Dicloxacillin Sodium monohydrate

DOSAGE FORM: Oral - Capsules

HOW DISPENSED
- [X] RX
- [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

dicloxacillin Sodium monohydrate
250 mg. and 500 mg Capsules

NAME OF APPLICANT *(Include City and State)*

Beecham Laboratories
Bristol, Tennessee

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Antibiotic

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME

DATE 12-31-79

FORM APPROVED BY

NAME Marcia Sevelle M.D.

DATE 12/31/79

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

MEMO FOR THE FILE

Form 6 #62-238

Mfg: Beecham Laboratories
Bristol, Tennessee

Drug: Dicloxacillin Sodium Monohydrate Capsules, 250 and 500 mg.

The formula and manufacturing procedures used to produce this product are the same as have previously been approved for Beecham Laboratories, Piscataway, New Jersey. The firm is in the process of moving all oral dosage penicillin products to the new facilities in Bristol, Tennessee.

Exhibit samples submitted for certification - satisfactory.
Comparative dissolution data - satisfactory.

Drug is packaged in identical container/closure system as authorized under Form 6 #60-254 (Piscataway).

GMP Status - satisfactory.
TWX from NSV-DO to HFD-322 dated 7/11/79.

William E. Magner
12/28/79

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Certifiable Drug Review Staff
Attn: William E. Magner (HFD-535)

DATE: December 21, 1979

FROM : Acting Deputy Director, NCAA (HFD-431)

SUBJECT: Beecham Laboratories
Dicloxacillin Sodium Capsules #62-238

The exhibit samples for the amendment to manufacture 250 mg. and 500 mg. dicloxacillin capsules in a new location have been tested and found to be satisfactory.

These samples were also tested for dissolution. Although we have no dissolution parameters for dicloxacillin capsules, the rapid solution of these capsules indicates that they pose no bioavailability problem.

The stability data submitted adequately support their request for a 5-year expiration dating.

George B. Selzer

Attachments

cc:
HFD-400
HFD-430 (2)
HFD-436 (2)
HFD-438
HFD-332

GBSelzer:mvs

CHEMISTRY REVIEW NOTES
DECEMBER 14, 1979

Re: Form 6, #62-238(Amendment)
Dicloxacillin Sodium Capsules
250mg and 500mg capsules
Submitted by Beecham

Beecham Laboratories is planning to manufacture sodium dicloxacillin capsules at its Bristol, Tenn. plant instead of its Piscataway, New Jersey facility.

The dicloxacillin sodium bulk will be manufactured in the New Jersey site. The suppliers of the magnesium stearate and the titanium dioxide are not identified.

The manufacturer has an approved Form 6 (61-822) for the dicloxacillin sodium bulk. The other raw ingredients conform to U.S.P. specifications.

It should be noted that the formulation for the 250mg capsule contains lactose which is not in the formulation of the 500mg capsule. The lactose is U.S.P. material and is adequately described.

All manufacturing processes are adequate. Specifications for the dosage form conform to CFR 440.119a.

Three exhibit lots were submitted. Lots MR937 and MM924 are for 500 mg capsules and lot MM923 for the 250mg capsules.

The results of our tests are satisfactory. The company's dissolution data were based on the rotating basket method at 50 R.PM in 900 ml water. Our laboratories used the rotating paddle at 50-100 r.pm in 900 ml water.

Dissolution by either method shows at least 90% of either size capsules to be dissolved in 30 mins. which is well above the limits for tetracycline hydrochloride capsules (used as a comparison). Limited stability data are presented for the 250mg capsule. Only two lots were studied over a five year period with storage at room temperature only.

Three lots of the 500mg size capsule show slight loss in chemical potency over the five year period. The manufacturer already has a five year expiration date for dicloxacillin sodium capsules produced at the New Jersey plant, and is requesting the same expiration date for capsules produced in the Bristol Tennessee plant. Such a request seems justifiable.

Results of our tests are within the limits of CFR 440.119a.

Time Spent - 60 hrs.
No. of tests- 35

Reviewed by _____

Jocelyn G. Blakely
ACB/NCAA

Beecham
laboratories

EXECUTIVE OFFICES 501 FIFTH STREET, BRISTOL, TENNESSEE 37620 615-764-5141

October 18, 1979

CERTIFIED MAIL #738920
RETURN RECEIPT REQUESTED

Food and Drug Administration
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

RE: #62-238 (440.119a)
Dicloxacillin Sodium Capsules

Gentlemen:

Reference is made to Beecham Laboratories Form 6 Antibiotic Application for Dycill (Dicloxacillin Sodium) Capsules, 500 mg.

We herewith submit an amendment to our Application to also provide for the manufacture of Dycill (Dicloxacillin Sodium) Capsules, 250 mg.

There are no changes in the methods and processes used in manufacturing, packing, labeling, assay and other controls used during the manufacture of the batch and after it is packaged for Dycill Capsules, 250 mg.,from that described in our Antibiotic Form 6 Application for Dycill Capsules, 500 mg., #62-238.

In support of this amendment, enclosed are the following items for the 250 mg. Dycill Capsules:

1) Production Formula
2) Specifications and Tests for Lactose, U.S.P. (an additional raw material used in the 250 mg. Capsule)
3) Packaging Specifications
4) Bottle Labels
5) Batch Quarantined and Approved Labels
6) Stability Data (60 Months)
7) Validation Data

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OCT 22 11 08 AM '79
FDA/DDU/HFD-535

Based upon the enclosed stability data, we are requesting an expiration date of 60 Months for the 250 mg. Dycill Capsules.

This submission is submitted in triplicate.

Sincerely,

Dennis R. Christian

Dennis R. Christian, Ph.D.
Director, Regulatory Affairs
DRC/hs
cc: FDA (3 copies)

010455

Beecham
laboratories

EXECUTIVE OFFICES 501 FIFTH STREET, BRISTOL, TENNESSEE 37620 615-764-5141

October 3, 1979

Mr. William E. Magner
Food and Drug Administration
Certifiable Drug Review Staff (HFD-535)
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

RE: Antibiotic Form 6 #62-238
Dicloxacillin Sodium Capsules

Dear Mr. Magner:

Enclosed please find (1) Antibiotic Form 7's for Dicloxacillin Sodium Capsules and (2) Dicloxacillin Sodium Capsules, 500 mg. for certification.

If there are any questions, please feel free to call me.

Sincerely,

Dennis R. Christian /hs

Dennis R. Christian, Ph.D.
Director, Regulatory Affairs

DRC/hs

Enclosures

cc: FDA (3 copies)
File (1 copy)

A-6
Harrison
Magnus

62-238

Beecham
laboratories

EXECUTIVE OFFICES 501 FIFTH STREET, BRISTOL, TENNESSEE 37620 615-764-5141

September 27, 1979

Food and Drug Administration
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

This Form 6 Application relates to the manufacture of Dicloxacillin Sodium Capsules, 500 mg. in our production facility located in Bristol, Tennessee, where the manufacture of all oral antibiotic dosage forms by Beecham Laboratories will take place in the future. These dosage forms are identical to those currently produced in our Piscataway Plant, the subject of an approved Form 6 (No. 60-254; 9-6-73).

It should be noted that the formula, raw material and finished product specifications, packaging specifications, labeling and testing methods employed for the production of Dicloxacillin Sodium Capsules in the Bristol, TN facility are all similar to those currently in use at the Piscataway, New Jersey Plant. The bulk dicloxacillin sodium (Bulk Master Blend) will continue to be manufactured at the Piscataway Plant (approved Form 6 No. 61-822) controlled at Piscataway, and forwarded to Bristol, TN. Beecham-Bristol has an approved Form 4 permitting receipt of uncertified bulks. All other controls will be exercised by the Quality Assurance unit in Bristol, TN.

RECEIVED
OCT 2
DRUG

In responding to the various items included in the standard Form 6 format, all control and validation procedures have been included. Thus, in effect, a substantial portion of the Master File (No. 3520) for this new plant is incorporated into this submission.

The plant site has been registered with the Food and Drug Administration.

The final section of this From 6 Application contains data derived from the production of one batch of dicloxacillin sodium capsules. Because the capsule formulation consists of 97% dicloxacillin sodium and 3% magnesium stearate, the distribution of magnesium stearate throughout the blend was chosen as the criteria indicating uniformity of blend. For a product of this type, proper functioning of the capsule-filling machine is the crucial factor in determining acceptability of the product and data generated during production

of this batch show performance is satisfactory. Antibiotic Form 6's, 62-212 (ampicillin trihydrate) and 62-216 (amoxicillin trihydrate) for 250 mg. and 500 mg. capsules, contain additional validation data further substantiating the blending and capsule filling operations.

Under approved Form 6 No. 60-254, Beecham Laboratories, Piscataway, New Jersey manufactured, packaged and labeled 500 mg. Dicloxacillin Sodium Capsules to be distributed by Ayerst Laboratories, New York, N.Y., under the tradename Veracillin.

We request approval to manufacture, package, and label 500 mg. Dicloxacillin Sodium Capsules at Beecham's Bristol, Tennessee Antibiotic Plant for distribution by Ayerst, under the tradename Veracillin. Labeling is included in Section 6 of the enclosed submission.

The manufacture of oxacillin capsules will be the subject of an additional Form 6 Application to be submitted in the near future.

Due to the operational complexities involved in transferring production from one site to another, we would appreciate your prompt consideration of this application. A desk copy of this submission is being forwarded to the Knoxville FDA Office.

Thank you for your cooperation.

Sincerely,

Dennis R. Christian / LB

Dennis R. Christian, Ph.D.
Director, Regulatory Affairs

DRC/hs

Attachment

cc: FDA (3 copies)
FDA Knoxville (1 copy)
File (1 copy)